UNIVERSIDADE FEDERAL DE SANTA CATARINA
CAMPUS ARARANGUÁ CENTRO DE CIÊNCIAS, TECNOLOGIA E SAÚDE
DEPARTAMENTO DE CIÊNCIAS DA SAÚDE
CURSO DE FISIOTERAPIA

GIORGIO SILVANO FERREIRA POLETTO

O EFEITO DO EXERCÍCIO FÍSICO AGUDO NOS NÍVEIS CIRCULANTES DE 2-ARAQUIDONILGLICEROL (2-AG) EM HUMANOS SAUDÁVEIS. UMA REVISÃO SISTEMÁTICA

Araranguá

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Trabalho Conclusão do Curso de Graduação em Fisioterapia do Centro de Ciências, Tecnologia e Saúde da Universidade Federal de Santa Catarina como requisito para a obtenção do título de Bacharel em Fisioterapia
Orientador: Prof., Dr Aderbal Aguiar Silva Júnior

Araranguá
2021

Ficha de identificação da obra elaborada pelo autor,
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Poletto, Giorgio Silvano Ferreira
O efeito do exercício físico agudo nos níveis circulantes de 2-araquidonilglicerol (2-AG) em humanos saudáveis. Uma revisão sistemática. / Giorgio Silvano Ferreira Poletto ; orientador, Aderbal Silva Aguiar Júnior, 2021.
50 p.

Trabalho de Conclusão de Curso (graduação) - Universidade Federal de Santa Catarina, Campus Araranguá, Graduação em Fisioterapia, Araranguá, 2021.

Inclui referências.

1. Fisioterapia. 2. Endocanabinóides. 3. Exercício físico. 4. Revisão sistemática. I. Júnior, Aderbal Silva Aguiar . II. Universidade Federal de Santa Catarina. Graduação em Fisioterapia. III. Título.

Giorgio Silvano Ferreira Poletto

Título: O efeito do exercício físico agudo nos níveis circulantes de 2-araquidonilglicerol (2-AG) em humanos saudáveis. Uma revisão sistemática.

Este Trabalho Conclusão de Curso foi julgado adequado para obtenção do Título de "Fisioterapeuta" e aprovado em sua forma final pelo Curso de Fisioterapia

Araranguá, 13 de Dezembro de 2021.

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Este trabalho é dedicado ao meu avô, Alfredo Nogueira Ferreira.

AGRADECIMENTOS

Agradeço a toda minha família, especialmente minha mãe, Lupe, que sempre esteve ao meu lado e me deu todo suporte emocional e financeiro para concluir o curso.

Ao meu avô, meu pai e meu irmão, que especialmente são os maiores exemplos que tenho em minha vida.

Às minhas amigas Camila, Naiara, Amanda, Leonara, Andressa, Thainá, Mariana e Larissa, por todo o amor e ensinamentos nesses anos de graduação.

Ao meu amigo Régis, pelo companheirismo, incentivo e conselhos nesses anos.

Ao meu orientador Aderbal Silva Aguiar Júnior e ao professor Alessandro Haupenthal, por todos os ensinamentos e oportunidades durante a graduação.

Por fim, a todas as pessoas que não mencionei que de alguma forma fizeram parte deste momento tão importante em minha vida.

RESUMO

O sistema endocanabinóide é responsável por diversos efeitos fisiológicos em nosso organismo. Estudos mostram a ativação desse sistema e o aumento de endocanabinóides circulantes em resposta ao exercício físico. O objetivo do presente estudo é sintetizar as evidências sobre o efeito agudo do exercício físico nos níveis circulantes de 2-araquidonilglicerol em humanos saudáveis. Para tal, foi conduzido uma revisão sistemática da literatura com análise do risco de viés. A presente revisão seguiu o checklist "Preferred Reporting Items for Systematic reviews and Meta-Analysis Protocols" (PRISMA-P) e seu protocolo foi devidamente registrado no "International Prospective Register of Systematic Reviews" (PROSPERO) sob número de registro: CRD42020202886. Os critérios de inclusão foram definidos pelo formato PICOS e os bancos de dados utilizados na pesquisa foram o US National Library of Medicine (PubMed), EMBASE, Web of Science, Cumulative Index to Nursing and Allied Health Literature (CINAHL), SPORTDiscus e Scopus, além da literatura cinzenta. Todas as etapas foram conduzidas de maneira independente e cega por dois pesquisadores (GP e VB). A seleção dos estudos e extração de dados foi realizada com auxílio das ferramentas EndNote Web e Ryann, além da confeção de uma planilha online para síntese das informações. Para análise do risco de viés dos estudos incluídos na revisão, foram utilizadas as ferramentas "Cochrane risk-of-bias tool for randomized trials (RoB2)", "The Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I)" e a ferramenta "JBI Critical Appraisal Checklist for Case Series" do instituto Joanna Briggs Institute (JBI). Ao final da busca, foram incluídos na revisão 12 artigos que analisaram a variação de 2-araquidonilglicerol em resposta ao exercício físico agudo.

Palavras-chave: Exercício. Atividade física. Endocanabinoides. Gliceril 2-araquidonato. 2 araquidonilglicerol. Sistema endocanabinoide. Nível de endocanabinoide no sangue. Revisão sistemática

LISTA DE FIGURAS

LISTA DE ABREVIATURAS E SIGLAS

2AG - 2-araquidonilglicerol

AEA - Anandamida

CB1 - Receptor canabinóide tipo 1

CB2 - Receptor canabinóide tipo 2

CINAHL - Cumulative index to nursing and allied health literature

ECR - Ensaio Clínico Randomizado

FCmáx - Frequência cardíaca máxima

IMC - Índice de massa corporal

JBI - Joanna Briggs Institute

MeSH - Medical subject headings

PICOS - Population-Intervention-Comparison-Outcomes-Study type

PRISMA-P - Preferred Reporting Items for Systematic reviews and Meta-Analysis Protocols

PROSPERO - International prospective register of systematic reviews

PubMed - US National Library of Medicine

RoB 2 - Revised cochrane risk of bias tool for randomized trials

ROBINS-I - Risk of bias in nonrandomized studies of interventions

SUMÁRIO

1. INTRODUÇÃO

A Anandamida ou n-araquidoniletanolamida (AEA) e o 2-araquidonilglicerol (2-AG) são os principais ligantes endógenos do sistema endocanabinóide. Além dos seus agonistas, o sistema endocanabinóide conta com receptores CB1 (tipo 1) e CB2 (tipo 2) (WATKINS, 2018). O sistema endocanabinóide desempenha um papel importante na modulação de diversos efeitos fisiológicos no nosso corpo, como por exemplo, o controle da dor (WOODHAMS *et al.*, 2017), a regulação do apetite (WITKAMP, 2018), a supressão da ativação de células inflamatórias (DONVITO *et al.*, 2017) e sensações de bem-estar, analgesia, sedação e euforia durante corridas de longa duração (FUSS, 2015; HICKS *et al.*, 2019; SIEBERS *et al.*, 2021). A principal fonte dos endocanabinóides é o sistema músculo esquelético, nele os endocanabinóides podem atuar promovendo a captação de glicose, melhora da ação da insulina e biogênese mitocondrial, consequentemente melhorando o desempenho e capacidade de exercício (HILLARD, 2018; HEYMAN; GAMELIN; AUCOUTURIER; DI MARZO, 2012b). Muitos estudos mostram que o exercício físico em diferentes intensidades tende a aumentar os níveis circulantes desses endocanabinóides (BRELLENTHIN, 2017; SCHONKE; MARTINEZ-TELLEZ; RENSEN, 2020). Brellenthin et al. (2017) observaram que a corrida prescrita em intensidade de 70 a 75% do VO2 máx durante 45 minutos e a corrida preferida (conforme preferencia do participante) foram capazes de aumentar os níveis circulantes de 2-AG em comparação à condição basal. Cedernaes e colaboradores (2016), também apresentaram que os níveis de 2-AG aumentaram imediatamente após 15 minutos de ciclismo em intensidade de 117W (75% VO2 de reserva). Corredores de longa duração vivenciam o fenômeno conhecido como “o barato do corredor”, caracterizado por sensação de euforia, sedação, ansiólise e hipoalgesia durante e após o exercício (SIEBERS, 2021). Estudos mostram que o barato do corredor está diretamente relacionado à ativação do sistema endocanabinóide que ocorre durante o exercício. (HICKS, 2018; SIEBERS, 2021; FUSS, 2015). Apesar da gama de estudos apresentados na literatura sobre o aumento da anandamida após o exercício físico, alguns estudos mostram controvérsias. Crombie et al. (2020) trouxeram que a corrida em intensidade de 73% da FC máx predita durante 30 minutos não foi capaz de alterar de maneira significante os níveis circulantes de 2-AG, levando a necessidade de uma melhor exploração deste sistema dentro da fisiologia do exercício. Até o momento, nenhum estudo estabeleceu uma revisão sistemática sobre a relação entre exercício físico agudo nos níveis de 2-araquidonilglicerol

circulante em humanos saudáveis. Assim, o presente estudo teve como objetivo sintetizar as evidências e determinar essa relação.

1.1 OBJETIVOS

Nas seções abaixo estão descritos o objetivo geral e os objetivos específicos deste TCC.

1.1.1 Objetivo Geral

O objetivo do presente estudo é sintetizar as evidências sobre o efeito agudo do exercício físico nos níveis circulantes de 2-araquidonilglicerol em humanos saudáveis.

1.1.2 Objetivos Específicos

Preparar um protocolo de revisão sistemática para investigar o efeito do exercício físico agudo nos níveis circulantes de 2-araquidonilglicerol em humanos saudáveis através de uma metodologia padronizada.

Sintetizar sistematicamente as evidências que avaliaram 2-araquidonilglicerol circulante em resposta ao exercício agudo em humanos saudáveis, de forma pareada, independente e cega.

Avaliar o risco de viés das evidências que avaliaram 2-araquidonilglicerol circulante em resposta ao exercício agudo em humanos saudáveis através de ferramentas recomendadas para cada tipo de estudo.

2 . METODOLOGIA

O presente estudo seguiu o checklist “Preferred Reporting Items for Systematic reviews and Meta-Analysis Protocols” (PRISMA-P) (SHAMSEER *et al.*, 2015) e o “Cochrane Handbook for Systematic Reviews of Interventions (Version 6)” (HIGGINS *et al*., 2019). O checklist PRISMA-P está disponível em anexo A. O protocolo da revisão sistemática foi registrada no “International Prospective Register of Systematic Reviews” (PROSPERO) sob número de registro: CRD42020202886.

2.1 TIPO DE ESTUDO

O presente estudo trata-se de uma revisão sistemática.

2.2 CRITÉRIO DE ELEGIBILIDADE

Os critérios de elegibilidade foram formulados de acordo com a estratégia PICOS: Population-Intervention-Comparison-Outcomes-Study type, conforme a população, intervenção, comparação, resultados e tipo de estudo.

2.2.1 População

Foram incluídos estudos com humanos, saudáveis, acima de 18 anos, treinados ou não. Não foram aplicadas restrições de gênero e etnia. Estudos com sujeitos não saudáveis, com fatores de risco ou que fizeram uso de substâncias psicotrópicas há pelo menos 7 dias antes do estudo foram excluídos. Foram incluídos sujeitos dos grupos controles ou com sujeitos submetidos a medicação placebo. Quando mais de um estudo utilizou dados da mesma amostra, foi considerado apenas o estudo com maior riqueza de detalhes. Foram excluídos os estudos que não trazem os dados a respeito das orientações relevantes sobre ingesta alimentar e exercício físico antes da intervenção ou do dia do teste.

2.2.2 Intervenção

Foram incluídos estudos que apresentaram como intervenção, atividade física ou exercício físico (incluindo uma única sessão), sem restrições do tipo (aeróbico, endurance), modalidade (caminhada, corrida, ciclismo, levantamento de peso), duração (semanas, meses), frequência (dias/semanas), duração da sessão (minutos), número de sessões, método de prescrição ou intensidade (lactato, percentuais da frequência cardíaca pico, frequência cardíaca de reserva,

limiares ventilatórios em teste cardiopulmonar, percentuais de força (Watt) e repetição máxima, esforço subjetivo (Borg) ou outros).

As intervenções que apresentaram recursos combinados (por exemplo, estratégias de mudanças de estilo de vida, como educação em saúde ou dieta / suplementação nutricional) foram excluídas.

Não foram aplicadas restrições quanto ao local de execução do estudo, bem como profissional da saúde que conduziu.

2.2.3 Comparação

Como comparador, foram incluídas as mensurações pré intervenção, os indivíduos que não participaram de nenhuma intervenção, ou a comparação entre duas intervenções concorrentes. As condições de controle que não foram relatadas ou não puderam ser calculadas foram excluídas

2.2.4 Resultados

Foram considerados os estudos que mensuraram os níveis circulantes de 2-araquidonilglicerol (2-AG) imediatamente (até 60 minutos) após o exercício físico. Estudos que quantificaram endocanabinóides em amostras salivares foram excluídos.

2.2.5 Tipo de estudo

Foram incluídos estudos experimentais (ensaios clínicos randomizados controlados (ECR) ou não controlados) ou quase experimentais e excluídos, estudos observacionais e revisões sistemáticas.

2.3 ESTRATÉGIA DE BUSCA

Uma pesquisa abrangente foi realizada nas seguintes bases de dados eletrônica: US National Library of Medicine (PubMed), EMBASE, Web of Science, Cumulative Index to Nursing and Allied Health Literature (CINAHL), SPORTDiscus e Scopus, sem limitações de idioma e publicado até março 2021. As buscas foram realizadas novamente antes da análise final. As pesquisas de estudos não publicados (literatura cinza) foram conduzidas usando OPEN GREY, Biblioteca Digital em Rede de Teses e Dissertações e ProQuest para identificar

qualquer informação adicional. As listas de referência dos estudos incluídos e revisões relevantes também foram analisadas manualmente, e especialistas no assunto também foram identificados e consultados para identificar potenciais estudos adicionais não incluídos nas pesquisas iniciais. A estratégia de pesquisa incluiu diferentes combinações com base em termos de cabeçalhos de assuntos médicos (Medical Subject Headings, MeSH) e palavras de texto livre e operadores booleanos para garantir a captura máxima de artigos.. A descrição da estratégia de busca inclui todas as modificações planejadas para os termos de indexação e palavras de texto livre que podem variar entre os bancos de dados. Uma bibliotecária documental (DMRP) corrigiu e implementou a estratégia de pesquisa e auxiliou nas ferramentas de seleção e avaliação dos estudos mencionados na revisão. Detalhes sobre os termos da estratégia de busca personalizados para cada base de dados estão descritos no apêndice A.

2.4 SELEÇÃO DOS ESTUDOS

Os estudos identificados foram importados para um software de manejo de referências (EndNote Web) e duplicatas foram eliminadas. Os títulos e resumos foram avaliados e rotulados como concordâncias/discordâncias em uma plataforma específica para autores de revisões sistemáticas (Rayyan). Este processo de seleção de estudos foi realizado de forma independente com cegamento por dois revisores (VB e GP) familiarizados com o tema de interesse para identificar estudos elegíveis. Nesta fase, os estudos considerados não relevantes (de acordo com os critérios de elegibilidade listados acima) foram excluídos. Eventuais inconsistências entre os revisores quanto à seleção foram resolvidas por um terceiro pesquisador (ASAJr) que decidiu.

2.5 EXTRAÇÃO DE DADOS

Um formulário de extração de dados elaborado no Microsoft Excel foi especificamente desenvolvido para esta revisão. Os dados extraídos foram preenchidos por dois revisores de forma independente com cegamento, incluindo detalhes sobre a publicação, desenho do estudo, características da população / intervenção e os resultados. Após a leitura dos artigos incluídos, foram extraídos os seguintes dados: detalhes da publicação (título, primeiro autor, país de investigação, ano de publicação, periódico, linguagem publicada); design do estudo (estudos experimentais ou quase experimentais); grupo/intervenção analisado (grupo controle

de estudos intervencionistas de doenças ou fatores de risco/grupo intervenção); características da população (fonte, tamanho amostral, critério elegibilidade, orientações pré-teste, sexo (%), idade [anos, média e desvio padrão (total amostral e/ou por grupo)], índice de massa corporal (IMC, kg/m2), nível de atividade física (treinado/não treinado), condição de saúde); mensuração de endocanabinóide (endocanabinoide, unidade de medida, parte do sangue (plasma/soro), estado alimentado ou jejum, tempo de coleta de sangue pós-exercício (min) e técnica extração e quantificação de 2-AG); características da intervenção e desenho experimental (número de participantes em cada grupo, tipo de intervenção, modalidade/ equipamento utilizado, método para determinar intensidade, protocolo, método de prescrição e intensidade, duração sessão (min), número de sessões experimentais, intervalo entre as sessões); comparador (repouso, intervenção concorrente ou linha de base) e resultados (níveis circulantes endocanabinoides, dados resumidos para cada grupo, diferença entre os grupos e/ou basal e pós-intervenção.

2.6 ANÁLISE DO RISCO DE VIÉS

Estudos clínicos randomizados foram analisados usando a ferramenta "Cochrane risk-of-bias tool for randomized trials (RoB2)" (STERNE *et al*., 2019). Todos os critérios pré estabelecidos pela ferramenta foram classificados em "baixo risco, algumas preocupações ou alto risco de viés". O risco de viés em estudos não randomizados ou estudos quase experimentais foi analisado pela ferramenta "The Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I)". Cada artigo foi avaliado nos diferentes domínios da ferramenta em "baixo risco, moderado risco, severo risco ou crítico risco de viés". A avaliação do risco de viés foi conduzida por dois avaliadores de forma independente e cega, e qualquer diferença foi resolvida por discussão e consenso. Além disso, foi utilizada a ferramenta "JBI Critical Appraisal Checklist for Case Series" para análise do risco de viés do "Joanna Briggs Institute (JBI)".

3. RESULTADOS

3.1 ESTUDOS INCLUÍDOS

Utilizando a estratégia de busca anteriormente citada, foram identificados 423 resultados. Os estudos em duplicata foram excluídos utilizando a plataforma Endnote, restando 250 estudos. Após a leitura do título e resumo desses estudos, foram selecionados 23 que se encaixam nos critérios de inclusão propostos na revisão. Em seguida, os artigos foram lidos na íntegra e foram excluídos 11 estudos que não se encaixavam nos critérios de inclusão, restando 12 artigos que analisaram a variação de 2-araquidonilglicerol em resposta ao exercício físico agudo (Figura 1) (HEYMAN *et al., 2012;* BRELLENTHIN *et al.*, 2017; CEDERNAES *et al.,* 2016; CROMBIE *et al*., 2018; CROMBIE *et al*., 2019; CROMBIE *et al*., 2020; RAICHLEN *et al.,* 2012; RAICHLEN *et al.,* 2013; SIEBERS, *et al.,* 2021; SPARLING *et al.,* 2003; HUGHES *et al.,* 2020; KOLTYN *et al.,* 2014). 6 desses 12 estudos apresentaram aumento nos níveis de 2-AG após a intervenção (BRELLENTHIN *et al.*, 2017; CROMBIE *et al*., 2018; CROMBIE *et al*., 2019; KOLTYN *et al.,* 2014; SIEBERS, *et al.,* 2021; CEDERNAES *et al.,* 2016), enquanto que outros 6 não apresentaram mudanças nos níveis de 2-AG após a intervenção (CROMBIE *et al*., 2020; HEYMAN *et al., 2012;* RAICHLEN *et al.,* 2012; RAICHLEN *et al.,* 2013; SPARLING *et al.,* 2003; HUGHES *et al.,* 2020)

Figura 1 - Características das intervenções dos estudos incluídos

	Autor, ano [país de investigação]	Método e protocolo para determinar intensidade	Protocolo intervenção	Resultados
Aeróbico/Longa duração				
	Brellenthin, 2017 [Estados Unidos]	Teste ergoespirométrico incremental submáximo Protocolo de Bruce: até atingir 85% FCmáx ajustada para a idade	**Corrida prescrita** Intensidade: 70 a 75% VO2máx estimado Baixa AFMV: 75,3 ± 8,6 Moderada AFMV: 72,1 ± 6,5 Alta AFMV: 68,6 ± 8,4 Volume: 45min [10min aquecimento (40% a 60%VO2máx estimado), 45min (70% a 75%VO2máx estimado), 5min resfriamento]	↑AEA e 2-AG 5min pós-corrida prescrita e preferida (P<0,01), com ↑AEA maior na condição prescrita (P<0,05)
	Cedernaes, 2016 [Suécia]	Teste ergoespirométrico incremental Protocolo: método do nomograma de Åstrands-Ryhming	**Ciclismo** Intensidade: 117 ± 10W (75% VO2 de reserva) Volume: 30min [5min aquecimento (25% da carga subsequente) + 30min (75% VO2 de reserva)	↑2-AG 15min pós-ciclismo (P<0,05) ↔AEA com tendência de aumento
	Crombie, 2018 [Estados Unidos]	Escala de esforço percebido de Borg	**Corrida** Intensidade: 78,90 ± 1,29% FCmáx predita; 7,56 ± 1,29 km/h (70 a 75% FCmáx predita; 12 a 15 na	↑AEA e 2-AG imediatamente pós-corrida (PS=0,000 a 0,050)

		escala de esforço percebido de Borg) Volume: 30min [10min aquecimento (40 a 60% FCmáx) + 30min (70 a 75%Fcmáx) + 5min de resfriamento]	
Crombie, 2019 [Estados Unidos]	Escala de esforço percebido de Borg	**Corrida** Intensidade: 160,7 ± 16,9 FC atingida no teste; 8,5 ± 1,7 km/h (70 a 75% FCmáx predita; 12 a 15 na escala de esforço percebido de Borg) Volume: 30min [5min aquecimento (40 a 60% FCmáx) + 30min (70 a 75%Fcmáx) + 5min de resfriamento]	↑AEA e 2-AG imediatamente pós-corrida (P<0,05)
Crombie, 2020 [Estados Unidos]	FCmáx ajustada para a idade	**Corrida** Intensidade: 73,82 ± 2,01% FCmáx predita; 6,82 ± 0,6 km/h (70 a 75% FCmáx predita) Volume: 30min [5min aquecimento (40 a 60% Fcmáx predita) + 30min (70 a 75%Fcmáx predita) + 5min de resfriamento] **Repouso**: posição sentada em silêncio por 40min em uma câmara com isolamento acústico	↔AEA e 2-AG imediatamente pós-corrida, com tendência de aumento pós-corrida, mas não após repouso
Heyman, 2012 [Bélgica]	Teste ergométrico incremental máximo Protocolo: 80W + 40W a cada 3 min até atingir exaustão	**Ciclismo** Intensidade: 55%Wmáx (moderado) + 75%Wmáx (intenso) (média amostral Wmáx= 330,7 ± 19,7) Volume: 15min repouso + 60min (55%Wmáx) + 30min (75%Wmáx) + 15min repouso	↑AEA imediatamente pós-ciclismo (P<0,01) e 15min após (P<0,001) ↔2-AG imediatamente pós-ciclismo
Raichlen, 2012 [Estados Unidos]	Velocidade selecionada pelo cálculo de Froude correspondente a determinada %FCmáx ajustada para a idade	**Corrida moderada** Intensidade: 2,5 ms^{-1}, 72,5 ± 2,54% FCmáx predita Volume: 30min **Caminhada leve** Intensidade: 1,25ms^{-1}, 44,6 ± 1,25% FCmáx predita Volume: 30min	↑AEA imediatamente pós-corrida (P<0,05) ↔AEA pós-caminhada com tendência de diminuir ↔2-AG em ambas as condições
Raichlen, 2013 [Estados Unidos]	FCmáx ajustada para a idade	**Caminhada moderada** Intensidade: 44,6 ± 4,16% FCmáx predita (<50% FCmáx predita) Volume: 30min **Corrida leve**	↑AEA imediatamente pós-corrida leve e moderada (P<0,05) ↔AEA pós-caminhada e corrida

			Intensidade: 72,48 ± 8,43% FCmáx predita (70% FCmáx predita) Volume: 30min **Corrida moderada** Intensidade: 83,23 ± 7,48% FCmáx predita (80% FCmáx predita) Volume: 30min **Corrida intensa** Intensidade: 92,1 ± 6,47% FCmáx predita (90% FCmáx predita) Volume: 30min	intensa com tendência de dimimuir ↔2-AG em todas as condições
	Siebers, 2021 [Alemanha]	FCmáx ajustada para a idade	**Corrida** Intensidade: 70-85% FCmáx predita Volume: 45min (opção de 5min aquecimento) **Caminhada** Intensidade: <50% FCmáx predita Volume: 45min	↑AEA e 2-AG imediatamente pós-corrida e caminhada, com aumento maior na condição corrida (P<0,001)
	Sparling, 2003 [Estados Unidos]	FCmáx ajustada para a idade	**Corrida** Intensidade: 70-80% FCmáx (140-160bpm) Volume: 45min [5min aquecimento + 45min (70-80% FCmáx)] **Ciclismo** Intensidade: 70-80% FC máx (140-160bpm) Volume: 45min [5min aquecimento + 45min (70-80% FCmáx)] **Repouso**: Posição sentada por 50min em uma sala com temperatura controlada	↑AEA imediatamente pós-corrida (P<0,01) e ciclismo (P<0,05) ↔AEA após repouso com tendência de diminuir ↔2-AG em todas as condições
Anaeróbico (Resistência muscular/curta duração)				
	Hughes, 2020 [Inglaterra]	Teste de 1RM; volume de exercício (kg) calculado pela repetição x carga de exercício (kg).	***Leg press* leve** Intensidade: 30% 1RM (47 ± 16kg) Volume: 3516 ±1168 kg 4 séries (30, 15, 15 e 15 repetições) com intervalos de 30s ***Leg press* intenso** Intensidade: 70% 1RM (109 ± 36kg) Volume: 4375 ± 1454 kg	↔2-AG após 5min de *leg press* leve e intenso, com tendência de diminuir após *leg press i*ntenso

		4 a 10 repetições com intervalos de 53s	
Koltyn, 2014 [Estados Unidos]	Teste de CMV	**Isométrico membro superior** Intensidade: 25%CMV braço dominante Volume: 3min	↑AEA e 2-AG imediatamente após exercício isométrico (P<0,05)

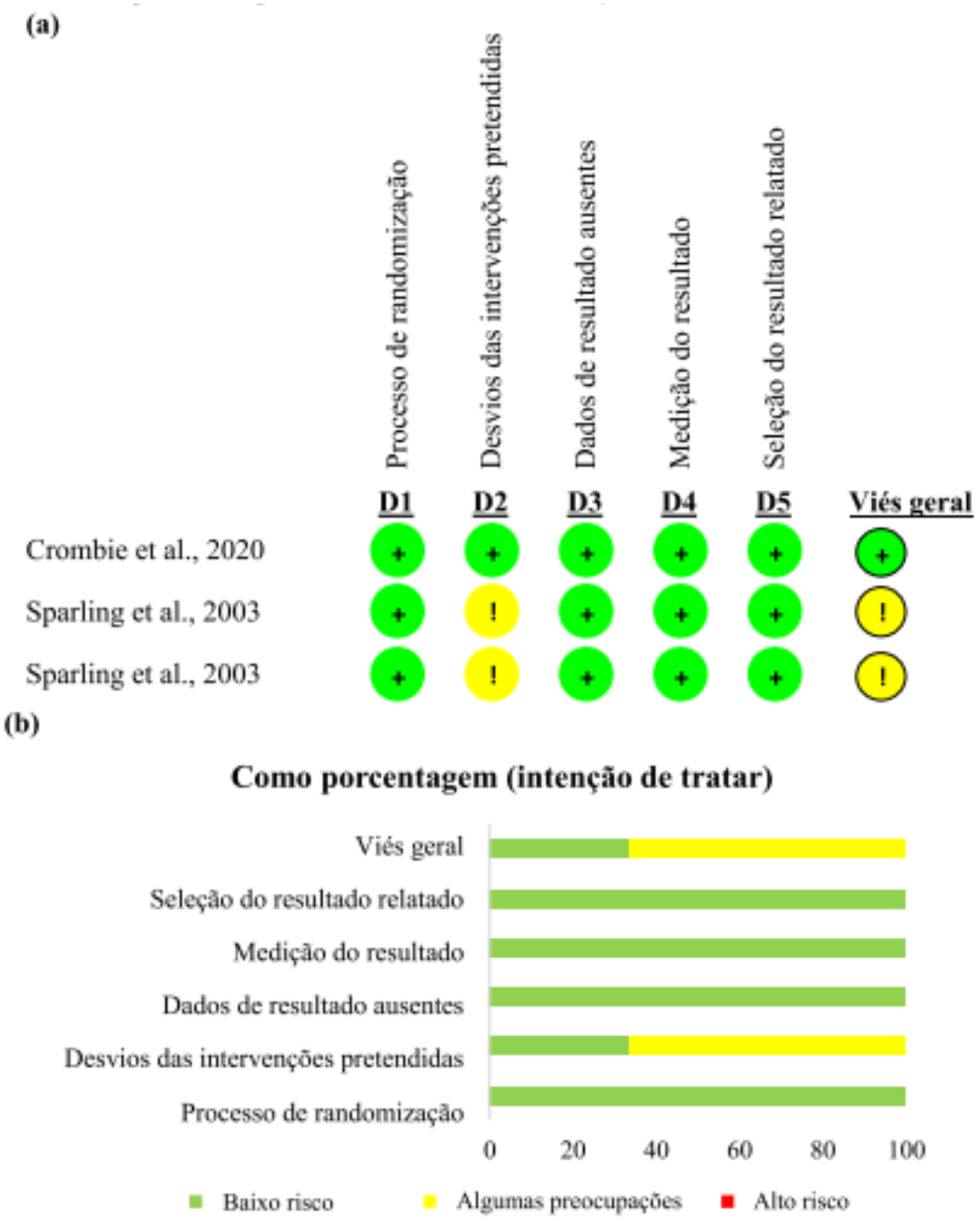
Fonte: Elaborada pela autora (2020). Legenda: AFMV= atividade física moderada-vigorosa; bpm= batimentos por minuto; CMV= contração máxima voluntária; FC= frequência cardíaca; FCmáx= frequência cardíaca máxima; LV= limiar ventilatório; VO2= volume de oxigênio; VO2máx= volume de oxigênio máximo; W= watt; 1RM= uma repetição máxima; ↑= aumento; ↔= sem efeito

3.2 ANÁLISE DO RISCO DE VIÉS

3.2.1 Estudos clínicos randomizados controlados

Os ECR que avaliaram o 2-AG apresentaram baixo risco de viés na maioria dos domínios (Figura 2). Apenas o estudo de Sparling et al. que investigou corrida e ciclismo mostrou algumas preocupações nos desvios das intenções pretendidas devido à ausência de análise estatística para estimar o efeito da atribuição à intervenção (SPARLING *et al*., 2003).

Figura 2 - Resultados da avaliação do risco de viés dos estudos incluídos usando a ferramenta da Cochrane de avaliação de risco de viés para estudos randomizados (Revised Cochrane risk of bias tool for randomized trials, RoB 2)



Fonte: Elaborada pela autora (2020). A ferramenta da colaboração Cochrane para avaliar o risco de viés dentro e entre os ensaios randomizados. (a) Risco de viés nos estudos; (b) Risco de viés entre os estudos.

A Figura 3 apresenta os resultados de cada estudo do tipo experimental não controlado para cada questão da ferramenta de avaliação do risco de viés JBI. A maioria dos estudos foi nomeada com "Y" de sim para cada questão específica, com exceção às questões:

1. **Q1** referente à clareza dos critérios de inclusão. No estudo de Hughes et al. não está claro os critérios de elegibilidade dos participantes, foi relatado ser não fumantes,

livres de algumas doenças e lesões musculoesqueléticas, da mesma forma, Raichlen et al., não relatou, somente incluiu homens e mulheres saudáveis, corredores regulares e aptos (HUGHES; PATTERSON, 2020; RAICHLEN; FOSTER; SEILLIER; GIUFFRIDA et al., 2013).

2. **Q4** referente à inclusão consecutiva dos participantes. Todos os estudos avaliados não relataram de forma consecutiva ou alguma descrição similar, contudo, os desenhos experimentais indicam e é usual na prática de pesquisas científicas realizarem a inclusão consecutiva num período coerente de tempo;
3. **Q5** referente à total inclusão dos participantes. Cedernaes et al. e Raichlen et al. relataram o N de indivíduos incluídos, porém, não especificaram se foi o total do recrutamento inicial (CEDERNAES; FANELLI; FAZZINI; PAGOTTO et al., 2016; RAICHLEN; FOSTER; SEILLIER; GIUFFRIDA et al., 2013).
4. **Q7** referente ao relato clínico dos pacientes. Considerando o nível de atividade física dos participantes, Cedernaes et al., Crombie et al. e Koltyn et al. não relataram estas informações clínicas (CEDERNAES; FANELLI; FAZZINI; PAGOTTO et al., 2016; CROMBIE; LEITZELAR; BRELLENTHIN; HILLARD et al., 2019; KOLTYN; BRELLENTHIN; COOK; SEHGAL et al., 2014).

Figura 3 - Resultados da avaliação do risco de viés dos estudos incluídos usando a ferramenta do Joanna Briggs Institute (JBI) para séries de casos / estudos não controlados (JBI Critical Appraisal Checklist for Case Series)

Estudo	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10
Brellenthin, 2017	Y	Y	Y	U	Y	Y	Y	Y	Y	Y
Cedernaes, 2016	Y	Y	Y	U	U	Y	N	Y	Y	Y
Crombie, 2019	Y	Y	Y	U	Y	Y	N	Y	Y	Y
Hughes, 2020	U	Y	Y	U	Y	Y	Y	Y	Y	Y
Koltyn, 2014	Y	Y	Y	U	Y	Y	N	Y	Y	Y
Raichlen, 2013	N	Y	Y	U	U	Y	Y	Y	Y	Y
Siebers, 2021	Y	Y	Y	U	Y	Y	Y	Y	Y	Y

Fonte: Elaborada pela autora (2020). Questões do instrumento do JBI, o Critical Appraisal Checklist for Case Series: Q1. Were there clear criteria for inclusion in the case series? Q2. Was the condition measured in a standard, reliable way for all participants included in the case series? Q3. Were valid methods used for identification of the condition for all participants included in the case series? Q4. Did the case series have consecutive inclusion of participants? Q5. Did the case series have complete inclusion of participants? Q6. Was there clear reporting of the demographics of the participants in the study? Q7. Was there clear reporting of clinical information of the participants? Q8. Were the outcomes or follow up results of cases clearly reported? Q9. Was there clear reporting of the presenting site(s)/clinic(s) demographic information? Q10. Was statistical analysis appropriate? Legenda: Y= yes (sim); N= no (não); U= unclear (confuso/pouco claro); NA= not applicable (não aplicável).

3.2.2 Estudos não randomizados

Os estudos não randomizados foram avaliados pela ferramenta ROBINS-I e apresentaram grandes limitações. Todos os estudos apresentaram fatores de confusão "sério" ou "moderado". Todos os outros itens apresentaram baixo risco de viés para os itens, conforme ilustrado na Figura 4. Na sequência, os confundidores estão detalhados para uma interpretação transparente e esclarecedora. Os confundidores relevantes para a configuração do estudo incluem tamanho amostral, intensidade e volume, nível de atividade física, adiposidade e dependência de exercício. No estudo de Crombie et al. foi considerado risco moderado de viés considerando os confundidores identificados pelos próprios autores como idade, sexo e nível de atividade física, todos controlados pelos critérios de elegibilidade e pareamento para ajustar o fator de confusão (CROMBIE *et al.,* 2018). A atividade física foi quantificada por sete dias através de acelerômetro, autorelato e apresentado o tempo sedentário e em atividade física leve e moderada. A adiposidade também foi controlada por meio do IMC. O viés geral do estudo de Heyman et al. foi julgado como sério risco de viés porque pelo menos dois domínio de confusão, tamanho amostral e nível de atividade física, não foram medidos (HEYMAN; *et al.*, 2012). O processo de recrutamento, seleção dos participantes e critérios de elegibilidade também não foram descritos. A intensidade e volume foram baseados em um teste ergométrico e estudos anteriores, além disso, a adiposidade foi medida através de peso e altura. No estudo de Raichlen et al. o julgamento implicou em sério risco de viés, dado que, os confundidores tamanho amostral, sexo, idade, nível de atividade física e adiposidade não foram medidos e controlados; apenas, intensidade e volume foram medidos, determinados pelo número de Froude e estudos anteriores (RAICHLEN *et al.*, 2012).

Figura 4 - Resultados da avaliação do risco de viés dos estudos incluídos usando a ferramenta de risco de viés em estudos de intervenção não randomizados (Risk Of Bias In Nonrandomized Studies of Interventions, ROBINS-I).

Fonte: Elaborada pela autora (2020). A ferramenta da colaboração Cochrane para avaliar o risco de viés nos ensaios não randomizados. (a) Risco de viés nos estudos sobre o resultado avaliado AEA; (b) Risco de viés nos estudos sobre o resultado avaliado 2-AG

4. CONCLUSÃO

Esta revisão sistemática fornece evidências de que o exercício agudo moderado é um contribuinte para o aumento dos níveis de 2-araquidonilglicerol circulantes, porém, o risco de viés e a heterogeneidade estatística dos estudos disponíveis podem limitar as conclusões. A partir disso, pesquisas adicionais são recomendadas para complementar esses achados usando um desenho randomizado controlado, amostras maiores e empregando estratégias para minimizar a influência de fatores de confusão como sexo, idade e nível de atividade física.

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APÊNDICE A – Estratégia de Busca personalizada de acordo com cada base de dado

Base de dados 1: PubMed

#1

"Exercise"[MeSH Terms] OR "Exercise"[Title/Abstract] OR "Exercises"[Title/Abstract] OR "Physical Activity"[Title/Abstract] OR "activities physical"[Title/Abstract] OR "activity physical"[Title/Abstract] OR "Physical Activities"[Title/Abstract] OR "exercise physical"[Title/Abstract] OR "exercises physical"[Title/Abstract] OR "Physical Exercise"[Title/Abstract] OR "Physical Exercises"[Title/Abstract] OR "Acute Exercise"[Title/Abstract] OR "Acute Exercises"[Title/Abstract] OR "exercise acute"[Title/Abstract] OR "exercises acute"[Title/Abstract] OR "exercise isometric"[Title/Abstract] OR "exercises isometric"[Title/Abstract] OR "Isometric Exercises"[Title/Abstract] OR "Isometric Exercise"[Title/Abstract] OR "exercise aerobic"[Title/Abstract] OR "Aerobic Exercise"[Title/Abstract] OR "Aerobic Exercises"[Title/Abstract] OR "exercises aerobic"[Title/Abstract] OR "Exercise Training"[Title/Abstract] OR "Exercise Trainings"[Title/Abstract] OR "training exercise"[Title/Abstract]

#2

"Endocannabinoids"[MeSH Terms] OR "Endocannabinoids"[Title/Abstract] OR "Endocannabinoid"[Title/Abstract] OR "2-arachidonoyl-glycerol"[Title/Abstract] OR "2-arachidonyl-glycerol"[Title/Abstract] OR "2-arachidonylglycerol"[Title/Abstract] OR "2-arachidonoylglycerol"[Title/Abstract]
OR "2-AG"[Title/Abstract] OR
"anandamide"[Title/Abstract] OR "n 2 hydroxyethyl arachidonamide"[Title/Abstract] OR "arachidonoyl ethanolamide"[Title/Abstract] OR "arachidonoylethanolamide"[Title/Abstract] OR "arachidonylethanolamide"[Title/Abstract] OR "5 8 11 14 eicosatetraenamide n 2 hydroxyethyl"[Title/Abstract] OR "anandamide 20 4 n 6"[Title/Abstract] OR "n-arachidonoylethanolamide"[Title/Abstract] OR "AEA"[Title/Abstract]

#3

"Adult"[MeSH Terms] OR "Adult"[Title/Abstract] OR "Adults"[Title/Abstract] OR "Young Adult"[MeSH Terms] OR "Young Adult"[Title/Abstract] OR "adult young"[Title/Abstract] OR "adults young"[Title/Abstract] OR "Young Adults"[Title/Abstract] OR "Middle Aged"[MeSH Terms] OR "Middle Aged"[Title/Abstract] OR "Middle Age"[Title/Abstract]
Base

Base de dados 2: EMBASE

#1

'exercise'/exp OR exercise:ab,ti OR 'aerobic exercise'/exp OR 'aerobic exercise':ab,ti OR 'exercise training':ab,ti OR 'exercise, aerobic':ab,ti OR 'exercise, isometric':ab,ti OR 'physical exercise':ab,ti OR 'isometric exercise'/exp OR 'isometric exercise':ab,ti OR 'physical activity'/exp OR 'physical activity':ab,ti OR 'activity, physical':ab,ti OR 'anaerobic exercise'/exp OR 'anaerobic exercise':ab,ti OR 'endurance training'/exp OR 'endurance training':ab,ti OR 'isokinetic exercise'/exp OR 'isokinetic exercise':ab,ti OR 'isotonic exercise'/exp OR 'isotonic exercise':ab,ti OR 'resistance training'/exp OR 'resistance training':ab,ti

#2

'endocannabinoid'/exp OR endocannabinoid:ab,ti OR endocannabinoids:ab,ti OR 'endogenous cannabinoid':ab,ti OR 'endocannabinoid system'/exp OR 'endocannabinoid system':ab,ti OR 'endocannabinoid 2 arachidonoylglycerol'/exp OR 'endocannabinoid 2 arachidonoylglycerol':ab,ti OR 'endocannabinoid blood level'/exp OR 'endocannabinoid blood level':ab,ti OR '2 arachidonoylglycerol'/exp OR '2 arachidonoylglycerol':ab,ti OR '2-arachidonylglycerol':ab,ti OR 'glyceryl 2 arachidonate'/exp OR 'glyceryl 2 arachidonate':ab,ti OR '2 arachidonoyl glycerol'/exp OR '2 arachidonoyl glycerol':ab,ti OR 'anandamide'/exp OR anandamide:ab,ti OR arachidonoylethanolamide:ab,ti OR arachidonylethanolamide:ab,ti OR (n:ab,ti AND '2 hydroxyethyl':ab,ti AND arachidonamide:ab,ti) OR 'n arachidonoylethanolamine':ab,ti

#3

'young adult'/exp OR 'young adult':ab,ti OR 'adult'/exp OR adult:ab,ti OR 'middle ages'/exp OR 'middle ages':ab,ti

Base de dados 3: Web of Science - Coleção Principal (Clarivate Analytics).

#1

TS=("Exercise"OR "Exercises" OR "Physical Activity" OR "Activities, Physical" OR " Activity, Physical" OR "Physical Activities" OR "Exercise, Physical" OR "Exercises, P hysical" OR "Physical Exercise" OR "Physical Exercises" OR "Acute Exercise" OR "Ac ute Exercises" OR "Exercise, Acute" OR "Exercises, Acute" OR "Exercise, Isometric" OR "Exercises, Isometric" OR "Isometric Exercises" OR "Isometric Exercise" OR "Exer cise, Aerobic" OR "Aerobic Exercise" OR "Aerobic Exercises" OR "Exercises, Aerobic " OR "Exercise Training" OR "Exercise Trainings" OR "Training, Exercise" OR "Traini ngs, Exercise")

#2

TS=("Endocannabinoids" OR "Endocannabinoid" OR "glyceryl 2-arachidonate" OR "2-arachidonoyl-glycerol" OR "2-monoarachidonoylglycerol" OR "2-arachidonyl- glycerol" OR "2-arachidonylglycerol" OR "5,8,11,14-eicosatetraenoic acid, 2-hydroxy-1-(hydroxymethyl)ethyl ester, (all-Z) -" OR "2-arachidonoylglycerol" OR "2- AG" OR "anandamide" OR "5,8,11,14-eicosatetraenoylethanolamide" OR "N-(2-hydroxyethyl)arachidonamide" OR "N-arachidonoyl-2- hydroxyethylamide" OR "arachidonoyl ethanolamide" OR "arachidonoylethanolamide" OR "arachidonylethanolamide" OR "5,8,11,14-eicosatetraenamide, N-(2-hydroxyethyl)- " OR "anandamide (20.4,n-6)" OR "n-arachidonoylethanolamide" OR "AEA")

#3

TS=("Adult"OR "Adults" OR "Young Adult" OR "Adult, Young" OR "Adults, Young" OR "Young Adults" OR "Middle Aged" OR "Middle Age")

Base de dados 4: CINAHL with Full Text (EBSCO).

1#

MH "Exercise" OR MH "Resistance Training" OR MH "Aerobic Exercises" OR TX "Aerobic Exercise" OR TX "Physical Exercise" OR TX "Exercise training" OR MH "Isometric Exercises" OR TX "Exercise, Isometric" OR TX "Exercises, Isometric" OR TX "Physical Exercise" OR MH "Physical Activity" OR TX "Physical Activities"

#2

TX "Endocannabinoid" OR TX "Endocannabinoids" OR TX "Endogenous cannabinoid OR TX "Endocannabinoid system" OR TX "Endocannabinoid 2 arachidonoylglycerol" OR TX "Endocannabinoid blood level" OR TX "Glyceryl 2-arachidonate" OR TX "2-arachidonoyl-glycerol" OR TX "2-AG" OR TX "Anandamide" OR TX "AEA" OR TX "n-arachidonoylethanolamide"

#3

MH "Adult" OR TX "Adults" OR MH "Young Adult" OR TX "Adult, Young" OR TX "Adults, Young" OR TX "Young Adults" OR MH "Middle Aged" OR TX "Middle Age"

Base de dados 5: SPORTDiscus with Full Text (EBSCO).

S1

TX "Exercise" OR TX "Resistance training" OR TX "Aerobic exercises" OR TX "Physical exercise" OR TX "Anaerobic exercises" OR TX "Isometric exercise" OR TX "Isotonic exercise" OR TX "Isokinetic exercise" OR TX "Physical activity" OR TX "Strength training" OR TX "Physical Activity"

S2

TX "endocannabinoid" OR TX "endocannabinoids" OR TX "endogenous cannabinoid" OR TX "endocannabinoid system" OR TX "endocannabinoid 2 arachidonoylglycerol" OR TX "endocannabinoid blood level" OR TX "glyceryl 2-arachidonate" OR TX "2-arachidonoyl-glycerol" OR TX "2-AG" OR TX "Anandamide" OR TX "AEA" OR TX "n-arachidonoylethanolamide"

S3

TX "Adult" OR TX "Adults" OR TX "Young Adult" OR TX "Adult, Young" OR TX "Adults, Young" OR TX "Young Adults" OR TX "Middle Aged" OR TX "Middle Age"

Base de dados 6: Scopus.

#1

(TITLE-ABS-KEY ("Exercise" OR "Exercises" OR "Physical Activity" OR "Activities, Physical" OR "Activity,

Physical" OR "Physical Activities" OR "Exercise, Physical" OR "Exercises, Physical" OR "Physical Exercise" OR "Physical Exercises" OR "Acute Exercise") OR TITLE-ABS-KEY ("AcuteExercises" OR "Exercise, Acute" OR "Exercises, Acute" OR "Exercise, Isometric" OR "Exercises, Isometric" OR "Isometric Exercises" OR "Isometric Exercise" OR "Exercise, Aerobic" OR "Aerobic Exercise" OR "Aerobic Exercises" OR "Exercises, Aerobic") OR TITLE-ABS- KEY ("Exercise Training" OR "Exercise Trainings" OR "Training, Exercise" OR "Traini ngs, Exercise"))

#2

(TITLE-ABS-KEY ("Endocannabinoids" OR "Endocannabinoid" OR "glyceryl 2-arachidonate" OR "2-arachidonoyl-glycerol" OR "2-monoarachidonoylglycerol" OR "2-arachidonyl-glycerol" OR "2-arachidonylglycerol") OR TITLE-ABS-KEY ("5,8,11,14-eicosatetraenoic acid, 2-hydroxy-1-(hydroxymethyl)ethyl ester, (all-Z)-" OR "2-arachidonoylglycerol" OR "2-AG" OR "anandamide" OR "5,8,11,14-eicosatetraenoylethanolamide" OR "N-(2-hydroxyethyl)arachidonamide") OR TITLE-ABS-KEY ("N-arachidonoyl-2-hydroxyethylamide" OR "arachidonoyl ethanolamide" OR "arachidonoylethanolamide" OR "arachidonylethanolamide" OR "5,8,1 1,14-eicosatetraenamide, N-(2-hydroxyethyl)-" OR "anandamide (20.4,n-6)" OR "n-arachidonoylethanolamide" OR "AEA"))

#3

TITLE-ABS-KEY ("Adult" OR "Adults" OR "Young Adult" OR "Adult, Young" OR "Adults, Young" OR "Young Adults" OR "Middle Aged" OR "Middle Age").

ANEXO A – PRISMA-P 2015 Checklist

This checklist has been adapted for use with systematic review protocol submissions to BioMed Central journals from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 4:1

An Editorial from the Editors-in-Chief of *Systematic Reviews* details why this checklist was adapted - Moher D, Stewart L & Shekelle P: Implementing PRISMA-P: recommendations for prospective authors. *Systematic Reviews* 2016 5:15

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	X	☐	2,3
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	X	Not applicable
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	X	☐	64
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide	X	☐	6-27

		physical mailing address of corresponding author			
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	X	☐	344-351
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	X	☐	114,115
Support					
Sources	5a	Indicate sources of financial or other support for the review	X	☐	335-338
Sponsor	5b	Provide name for the review funder and/or sponsor	X	☐	335-338
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	X	☐	338-341
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	X	☐	72-106
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	X	☐	102-106

METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	X	☐	118-163
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	X	☐	166-174
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	X	☐	174-181 (Addition file 2)
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	X	☐	187-190;205
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	X	☐	206,207; 232,233; 277,278
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	X	☐	205,208

Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	X	☐	210 (Table 1)
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	X	☐	215-219
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	X	☐	222,227
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	X	☐	236,237
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	X	☐	256-264
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	X	☐	265-269
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	X	☐	240-242

Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	X	☐	270-274
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	X	☐	277-284

ANEXO B – Protocolo para condução da revisão sistemática

Title

The effects of physical exercise on circulating levels of endocannabinoids - a protocol for a systematic review and meta-analysis

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ABSTRACT

Background: Exercise increases the circulating endocannabinoids. This phenomenon is associated with runner's high, a state of euphoria and well-being experienced after long exercise. We will provide in this review a transparent and standardized methodology for conducting a systematic review and meta-analysis for synthesizing the available evidence on the effects of physical activity on the circulating levels of endocannabinoids in healthy subjects.

Methods: PubMed, EMBASE, Web of Science, CINAHL, SPORTDiscus, and Scopus will be the databases. Search strategies will combine medical subject headings terms and free text words, including "exercise" "exercise, physical," "exercise training," "physical activity," "endocannabinoids," "2-arachidonoyl-glycerol," "glyceryl 2-arachidonate," "2-AG," "anandamide," "AEA," "n-arachidonoylethanolamide," "adult," "young adult," and "middle-aged." We will select experimental or quasi-experimental studies published through March 2021. The selection of studies, data extraction, assessment of the risk of bias, and the quality of evidence will be carried out in a paired and independent manner, and the consistency will be assessed using the statistics of Cohen Kappa. Methodological quality will be assessed using the Revised Cochrane risk of bias tool for randomized trials (RoB 2) and the Risk Of Bias In Nonrandomized Studies of Interventions (ROBINS-I) risk tool. We will use the Grading of Recommendations Assessment, Development, and Evaluation to assess the evidence's quality, x2 and I2 tests for heterogeneity, funnel plots and Egger test for

publication bias. A meta-analysis for each data comparison will be performed whenever possible to determine the effect of physical activity on the circulating levels of endocannabinoids.

Discussion: This systematic review and meta-analysis will provide an overview of the evidence in the field of physical activity and endocannabinoid research including comparability of variables between studies, critical interpretation of results and use of accurate statistical techniques. Thus, this study will determine the acute effect of physical exercise on circulating levels of endocannabinoids in healthy individuals. The results of this study will potentially be transferred to doctors, health professionals and legislators to guide their decision making, as well as, will improve future research

Systematic review registration:
PROSPERO CRD42020202886.

Keywords: exercise; physical activity; endocannabinoids; glyceryl 2-arachidonate; 2 arachidonoylglycerol; anandamide; n arachidonoylethanolamine; endocannabinoid system; endocannabinoid blood level; systematic review.

BACKGROUND

Anandamide or n-arachidonylethanolamide (AEA) and 2-arachidonylglycerol (2-AG) are endogenous cannabinoids for the G-protein-coupled cannabinoid receptors CB1 (type 1) and CB2 (type 2) (1). The endocannabinoid system plays a crucial role in the maintenance of homeostasis in thermoregulation and motor control (2), energy metabolism (3), skin function (barrier formation, regeneration) (4), appetite and digestion (5), learning and memory (6), chronic pain (7), inflammation and other immune system responses (8). Endurance running and cycling increase the circulating AEA and 2-AG produced by contracting muscles (9-12). During/after a long run, AEA and 2-AG induce a state of euphoria, known as the runner's high (13). However, there are controversies regarding the required exercise intensity to produce this effect (12, 14, 15). Moreover, these effects are

different for upper limb exercises. Long durations of arm exercises reduce circulating AEA, and resistance arm exercises do not affect 2-AG (14, 15).

Literature reviews have focused on the effect of physical activity on the endocannabinoid system and its impact on the pathology of neurological and neurodegenerative diseases, such as depression, anxiety, multiple sclerosis, epilepsy, Parkinson's and Alzheimer's disease, in animal and human models (9, 16, 17). They also addressed the benefits of exercise-induced endocannabinoid changes on brain function (cognition, mood, appetite, reward system), the musculoskeletal and adipose tissue (glucose regulation, insulin sensitivity, lipogenesis), and stress (18-20). Moreover, Hillard (11) compiled information on circulating endocannabinoid levels and metabolic regulation, sleep, inflammation, and exercise. These were reviews of adaptations of the endocannabinoid system to physical activity with implications for health and well-being.

However, there are no reviews on the acute effects of physical activity on circulating endocannabinoids, a transient effect with significant biological effects. The acute and training effects (adaptations) of physical exercise are the two main exercise physiology objectives. A systematic review uses a methodology that aims to gather all relevant evidence, based on predefined eligibility criteria, to answer a specific research question (21). The use of statistical techniques such as meta-analysis can combine and summarize the results to provide more accurate estimates of individual studies' effects (21). In this context, this protocol implies prior documentation that allows for anticipating possible problems and improving planning before the review. A methodical and analytical approach will be employed. The purpose of this study protocol is to provide a transparent and standardized methodology for conducting a systematic review and meta-analysis in order to synthesize the available evidence and determine the effects of acute physical activity on the circulating levels of endocannabinoids in healthy subjects.

METHODS/DESIGN

This protocol follows the Preferred Reporting Items for Systematic reviews and Meta-Analysis Protocols (PRISMA-P) (21) and the Cochrane Handbook for Systematic Reviews of Interventions (Version 6) (22). The PRISMA-P Checklist can be found in the

Additional file 1. We registered in the International Prospective Register of Systematic Reviews (PROSPERO) (registration number: CRD42020202886). Any changes to this protocol will be described in the final review.

Eligibility criteria

The eligibility criteria are under the Population-Intervention-Comparison-Outcomes-Study type (PICOS):

Population

We will include studies with healthy humans, adults over 18, trained or not (23). Including individuals need to be submitted to placebo medication or included in control groups of interventional studies on diseases/risk factors, since both placebo and control groups can be considered similar enough to be combined for synthesis (24). No gender or ethnicity restrictions should apply. When more than one study provides data from the same sample, we will consider only the study that presents the most detailed results concerning its eligibility.

Studies carried out with unhealthy subjects or with factors that can interfere with the reliability of the results, such as the use of psychotropic substances in the last seven days (for example, synthetic cannabis/cannabis, cocaine, methamphetamine, ecstasy, and others) and the absence of relevant guidelines before the day of the test and/or intervention about food and exercise will be excluded.

Intervention

Studies will be eligible if presented as an intervention, physical activity, or exercise (including a single session), regardless of its type (aerobic, muscular endurance), modality (walking, running, cycling, free weights), duration (week, months), frequency (days/week), session duration (minutes), number of sessions, prescription methods, or intensity [lactate, percentages of peak heart rate (peak HR), reserve HR (Karvonen), ventilatory thresholds in the cardiopulmonary test, percentage of power (Watt) and maximum repetition, subjective feeling of effort (Borg), others] (25). The World Health Organization (23) defines physical activity as "anybody movement produced by skeletal muscles that require energy expenditure." Exercise is defined as planned, structured, regular physical activity aiming to improve or maintain physical fitness.

No restrictions will be imposed regarding supervision (in person or not), the location of the intervention (clinic/health center, hospital, university, other), the type of performance (individual, group), or the specialization of the professionals who provided the physical activity or exercise (physiotherapist, fitness instructor, exercise scientist, other).

Interventions that feature combined resources (for example, lifestyle change strategies, such as health education or diet/nutritional supplementation) will be excluded.

Comparison

Control conditions will be included, covering a control group comprised of individuals who did not participate in any form of intervention, or comparisons of the results obtained between the baseline and immediately after the intervention or recovery period. Control conditions that are not reported or cannot be calculated will be excluded.

Outcomes

We will include studies that evaluated circulating levels of endocannabinoids (AEA and 2-AG), immediately after the end of the intervention, without restriction to primary or secondary outcomes. These measures are considered a physiological response or acute effect of physical activity or exercise. Studies with measurements of salivary endocannabinoids or other endogenous ligands will not be included.

Study type

Experimental studies (randomized or controlled clinical trials) or quasi-experimental and excluded studies, observational studies, and systematic reviews will be included.

Search strategy

These are the future electronic databases of the comprehensive search: US National Library of Medicine (PubMed), EMBASE, Web of Science, Cumulative Index to Nursing and Allied Health Literature (CINAHL), SPORTDiscus, and Scopus, without language limitations and published through March 2021. The searches will be conducted again before the final analysis. Searches for unpublished studies (gray literature) will be conducted using OPEN GRAY, Networked Digital Library of Theses and Dissertation, and ProQuest to identify any further information. The reference lists of the included studies and relevant reviews will also be analyzed manually, and specialists in the subject will also be identified and consulted to identify potential additional studies not included in the initial searches. The search strategy

will include different combinations based on medical subject headings terms and free text words and Boolean operators to ensure maximum capture of articles, including: "exercise," "exercise, physical," "exercise training," "physical activity," "endocannabinoids," "2-arachidonoyl-glycerol," "glyceryl 2-arachidonate," "2-AG," "anandamide," "AEA," "n-arachidonoylethanolamide," "adult," "young adult," and "middle-aged." The preliminary search strategies were developed and tested in a pilot, adapted according to each database (Additional file 2). The search strategy description includes all planned modifications to the indexing terms and free text words that may vary between databases. A documentary librarian (DMRP) wrote and implemented the research strategy and assisted in the selection and evaluation tools of the studies mentioned below.

Selection of studies

The identified studies will be imported into reference management software (EndNote Web), and duplicate records will be deleted. Titles and abstracts will be evaluated and labeled agreements/disagreements on a specific platform for authors of systematic reviews (Rayyan) (26). This study selection process will be carried out independently with blinding by two reviewers (VB and GP) familiar with the topic of interest to identify eligible studies. There will be no blinding to authors, institutions, or journals of the reviewed articles during the selection of studies. Abstracts that do not provide sufficient information on the eligibility criteria will be selected for a more detailed evaluation by reading the article's full text. The reviewers will then examine the articles to be included in a paired, independent, and blinded way, in the original format in full text, and available in full in each database. At this stage, studies considered not relevant (according to the eligibility criteria listed above) will be excluded, and we will record the corresponding reason in the article selection flowchart. Any inconsistencies between the reviewers regarding the selection will be resolved by a third researcher (ASAJr) who will decide. The selection process of the eligible studies shown in the PRISMA Flowchart provides an idea about the search strategy's scope and increases the internal validity of the review.

Data extraction

A data extraction form prepared in Microsoft Excel was explicitly developed for this review (Table 1). The extracted data will be filled in by two reviewers independently with

blinding, including details about the publication, study design, characteristics of the population/intervention, and the results.

Insert Table 1

After reading the included articles, additional data will be extracted when considered essential for the interpretation and applicability of the results; for example, the methods used for analyzing the endocannabinoids. In cases of missing data, the authors of the studies will be contacted by e-mail. If no response is received, the study will be excluded. Results data that meet the inclusion criteria will be extracted, including baseline values, immediately after the intervention and/or recovery period from the exercise, and the mean values and postintervention standard deviation. The values of P, interquartile range (IQR), standard error, and interval confidence will be extracted, if available.

Bias risk assessment

Randomized clinical trials will be evaluated using the Revised Cochrane risk-of-bias tool for randomized trials (RoB2) (27). This tool covers the following criteria: randomization process, deviations from the intended interventions, missing results data, measurement of the results, selection of the reported result, and general bias. Each criterion will be evaluated and scored as low risk, some concerns, or a high risk of bias.

The Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool will assess the risk of bias in nonrandomized and quasi-experimental studies (28) will be used. The domains comprise confusion, selection of study participants, classification of interventions, deviations from intended interventions, missing data, measurement of results, and selecting the reported result. It can be classified as without information, low risk, moderate, severe, or critical. The risk of bias assessment will be carried out by two assessors independently, and any differences will be resolved by discussion and consensus.

Data synthesis and analysis

The included studies will be stratified by type of intervention and outcome measures and analyzed separately, based on the study design. The level of agreement between the two

authors at each stage of the review (selection of studies, data extraction, assessment of the risk of bias and quality of evidence) will be assessed using Cohen Kappa statistics. The closer this statistic is to 1, the higher the agreement among reviewers. The included studies will be summarized in an Ad Hoc table for comparison and assistance in critical interpretation. Whenever possible, we will use the results from an intention‐to‐treat analysis.

With the recorded results data, the meta-analysis can be calculated for each data comparison, if applicable. The results will be recorded in tables and/or graphs that describe data such as means and standard deviation (from data obtained from the studies or calculated), the effect size as a standardized mean difference with 95% CI and study weighting. The forest plots will be created using Review Manager software (RevMan 5.4) (29) to illustrate the individual and grouped effect sizes. The standardized mean difference will be calculated as the difference in means between the values (baseline/postintervention and/or intervention/control) divided by the pooled standard deviation of the measurements. For this study, the effect size will be categorized as follows: small (ranging from 0 to 0.2), moderate (ranging from 0.2 to 0.5), and large (ranging from 0.5 to 0.8). The studies' weighting effect will be calculated using the inverse variance method (individual effect sizes multiplied by the inverse of their standard squared error) to reflect individual studies' contribution to the total effect estimate.

The heterogeneity assessment will include the 2 test to verify heterogeneity, with a significance level of $p < 0.10$. The magnitude of the heterogeneity of each meta-analysis will be quantified by the I2 statistic, interpreted as follows: might not be essential (0%– 40%), moderate (30%– 60%), substantial (50%– 90%), and considerable (75%– 100%). If I2 is ≤50%, the fixed-effects model (Mantel-Haenszel method) will be used for the meta-analysis. Although an I2 >50% is considered representative, indicating significant heterogeneity, the random-effects model (DerSimonian and Laird method) will collect the results. Considering the possibility of high heterogeneity, we will analyze its possible sources to obtain an objective conclusion.

The analysis of the source of heterogeneity (sensitivity, subgroup and/or meta-regression analysis) will be defined only during the review process, where the peculiarities of the included studies will be identified, such as sample size, sex, age, overload principle (intensity versus volume), adaptation to exercise, randomization, missing data, and other relevant situations.

The funnel plot will be used to assess publication bias, and the Egger test will check the asymmetry of plotting the funnel. Asymmetric funnel plots indicate publication bias, which is a reporting bias, but it also implies that there may be other causes, such as differences in methodological quality or heterogeneous effects of the intervention. We will review the possible reasons and explain any asymmetric funnel plot.

Assessment of the quality of the evidence

The analysis of the quality of the evidence will be conducted in a paired and independent way using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) (30, 31). The GRADE tool consists of the following criteria: methodological limitations (risk of bias), inconsistent results, indirect evidence, imprecision, and publication bias. For each analyzed result, the evidence's quality will be classified as very low, low, moderate, or high using the GRADE profiler (GRADEpro) Guideline Development Tool (32). Disagreements will be resolved by discussion and consensus. The results will be presented in a "Summary of Findings" table.

DISCUSSION

This review will be the first to systematically identify and analyze evidence on the acute effects of physical activity on circulating levels of endocannabinoids. The assessment of the risk of bias, the quality of evidence, and heterogeneity, with particular reference to the sample's characteristics, is a point highlighted in this review. This protocol presents an explicit and replicable methodology through the search strategy, study selection, and data extraction, in addition to synthesizing the data using meta-analyses. This study will provide an overview of the evidence available to avoid duplication of research. It will also identify possible knowledge gaps and inform experimental protocols in the field of physical activity and endocannabinoid research. It will guide recommendations on the effectiveness of physical activity on the endocannabinoid system to improve future research. Above all, this study's results will provide the highest level of evidence that can potentially be transferred to clinicians, healthcare professionals, and policymakers to guide their decision making.

List of abbreviations

AEA n-arachidonylethanolamide

2-AG 2-arachidonylglycerol

CB1 Cannabinoid receptors type 1

CB2 Cannabinoid receptors type 2

PRISMA-P Preferred Reporting Items for Systematic reviews and Meta-Analysis Protocols

PROSPERO International prospective register of systematic reviews

PICOS Population-Intervention-Comparison-Outcomes-Study type

HR Heart Rate

PubMed US National Library of Medicine

CINAHL Cumulative Index to Nursing and Allied Health Literature

IQR interquartile range

RoB2 Revised Cochrane risk-of-bias tool for randomized trials

ROBINS-1 Risk Of Bias In Non-randomized Studies of Interventions

RevMan Review Manager

GRADE Grading of Recommendations Assessment, Development, and Evaluation

GRADEpro Grading of Recommendations Assessment, Development, and Evaluation profiler

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

Competing interests

The authors declare that they have no competing interests

Funding

Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) - Financial Code 1, Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), and the Fundação de Amparo à Pesquisa e Inovação do Estado de Santa Catarina (FAPESC) financially supported the production of this protocol. The funding will support data collection, management, and data analysis carried out by researchers through grants and capital. The funders will not be involved in any other aspect of the study, such as protocol design, interpretation, or the publication of results.

Authors' contributions

VB and ASAJr designed and drafted the protocol. VB and DMRP developed the search strategy and defined the assessment tools for the studies. VB and GP conducted the pilot search in the databases assisted by DMRP. VB developed the data extraction form and the procedures adopted for data synthesis and analysis of results. ASAJr and IJCS performed a critical review of the manuscript, statistical analysis, and data synthesis. GP enabled the inclusion of RevMan software in the methodology. ASAJr coordinated the study. All authors contributed to the revision/editing of the protocol and agreed with the final version of this review protocol. VB is the guarantor of the review.

Acknowledgements

We thank Karyn Munik Lehmkuhl (UFSC) for supporting the methodology.

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Additional file

File name: Additional file 1.

File format: Microsoft Word (DOC)

Title of data: The PRISMA-P Checklist

Description of data: The PRISMA-P checklist adapted for use with systematic review protocol submissions to BioMed Central journals.

File name: Additional file 2.

File format: Microsoft Word (DOC)

Title of data: The search strategies at the electronic databases.

Description of data: The preliminary search strategies, developed and tested in a pilot, adapted according to each database.

Table 1. Characteristics of the studies included in the systematic review and meta-analysis.

Intervention characteristics

Results

Publication details Study design Population characteristics Physical activity or exercise Circulating endocannabinoid levels

Title, first author, country of research, year of publication, journal, published language. Experimental (randomized or controlled clinical trials) or quasi-experimental studies. Source, sample size, eligibility criteria, sex (%), age (years, mean and standard deviation (total sample and / or by group)). Physical activity level (trained / untrained), health condition. Number of participants in each group and type of intervention (anaerobic, aerobic, interval). Protocol (intensity [lactate, percentages of peak heart rate (peak HR), reserve HR (Karvonen), ventilatory thresholds in the cardiopulmonary test, percentage of power (Watt) and maximum repetition, subjective feeling of effort (Borg), others], session duration (minutes), session frequency, intervention duration (weeks)).

Summary data for each group, difference between groups and / or change between baseline and post-intervention (mean and standard deviation, P value, interquartile range, standard error and / or interval confidence).

ANEXO C – Normas de Submissão da Revista “Systematic Reviews"

Submission Guidelines

Preparing your manuscript

This section provides general style and formatting information only. Formatting guidelines for specific article types can be found below.

- Research
- Methodology
- Protocol
- Commentary
- Letter
- Systematic review update

General formatting guidelines

- Preparing main manuscript text
- Preparing illustrations and figures
- Preparing tables
- Preparing additional files

Preparing figures

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